DuPont
Performance Elastomers

January 21, 2010

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CC: **Docket ID No. EPA-HQ-ORD-2009-0217**
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Dear Mr. Davis:

DuPont Performance Elastomers (DPE) thanks the USEPA for the opportunity to present its positions at the Chloroprene External Peer Review Panel (Panel) meeting held on January 6, 2010.

While we appreciate the opportunity to express our views as part of the written record, issues were raised during the public Peer Review Panel meeting to which we were not permitted to respond. As described in our prior written and oral comments, the goal of DuPont Performance Elastomers, in collaboration with our International Institute of Synthetic Rubber Producers partners, has been to identify, conduct and communicate research supporting development of a scientifically sound and complete risk assessment for chloroprene. Consequently, we are providing you, as the IRIS Chemical Manager for chloroprene, with additional comments on points discussed during the Panel meeting where we both agree and disagree with Panel Member statements. In principle, we agreed with several points discussed by the Panel, notably

- Oral RfD values cannot be calculated from the existing data and route to route extrapolation cannot be conducted, since no validated oral kinetic data are available.
- In considering the species and effect used in the derivation of the RfC, we support the position that the most sensitive and relevant endpoint for chloroprene should be selected prior to any dose adjustment in dose-response modeling to define the Point of Departure (POD).

- Consideration of the rat as the more appropriate species for cancer risk assessment, given the questionable relevance of the mouse bronchioalveolar tumors to humans and the similar kinetics of chloroprene metabolism in the rat and human, compared to the mouse.
- Including an upper bound cancer risk estimate based on exposure data described in the Marsh et al. (2007a, b) epidemiology study to compare with the unit risk estimates derived using either the mouse or the rat data.
- We agree and see value in the use of models for HEC derivation. Using a validated PBTK model for chloroprene, as will be reported in the results of the forthcoming IISRP studies, will provide a robust approach to quantitatively account for the differences in toxicokinetics between rodents and humans.
- The lack of consideration of the DeWoskin (2007) peer-reviewed manuscript in the Draft Review was noted.

There remain a number of topics where our understanding of the science differs from the verbal positions articulated by the Panel. The issues which we believe merit a more in-depth scientific review include:

Evaluation of Epidemiological Data

- **It is inappropriate for the USEPA and the Panel Members to reach weight-of-evidence conclusions without understanding the limitations of the Eastern European and Asian epidemiology studies compared to the strengths identified with the Marsh et al. (2007) US and Western European epidemiology studies when using the 2005 USEPA criteria for evaluation of epidemiology study quality.**

We believe it is inappropriate for the USEPA to give equal weighting to the Eastern European and Asian epidemiology studies (Bulbulyan et al., 1998, 1999; Li et al. 1989) as that accorded to the key study conducted by Marsh et al. (2007a,b). As noted by multiple commenters, the Marsh et al. study provided the most complete and robust study of chloroprene human cancer risk to date. Further, an independent review of chloroprene epidemiology published by Bukowski (2009) that directly applies USEPA guidelines for assigning weight-of-evidence to epidemiologic studies should be included in the Draft Toxicological Review.

With respect to the weight-of-evidence discussions, we believe that the positions articulated by Panel Members misinterpret the significance of the Marsh et al study (2007a, b) by not appreciating: a) the lack of monotonic dose response and statistical significance in the relative risks (RR) for lung and liver cancers; and b) that the apparent increase in RR for lung and liver cancer as a function of chloroprene exposure is misleading without considering the impact of the spuriously low cancer deficits in the baseline population. Dr. Marsh provided further information at the Panel meeting and in the DPE written comments to conclude that there is no association between chloroprene exposure and liver or lung cancer.

In addition, it is scientifically indefensible to selectively use results from the Marsh et al. (2007a,b) study to present alternate interpretations of potential excess cancer risk that deviate from the conclusions published by the study authors. Revising the conclusions of the original authors of a published peer-reviewed study demands a comprehensive and justifiable rationale for doing so. Such a rationale was not provided in either the Draft Toxicological Review nor by Panel Members.

Overall, we maintain that the conclusions of the Marsh et al. (2007a,b) study should prevail in a weight-of-evidence analysis that considers the limitations of previous epidemiological investigations; in brief, the overall weight-of-evidence does not support the conclusion that chloroprene is "likely to be carcinogenic to humans".

- **One Panel Member indicated that it was not possible to evaluate fully exposure-response in the Marsh *et al.* cohort study because the study investigators "had not performed lagged analyses or analyses by age at onset".**

This statement is incorrect because extensive lagged analyses were conducted as reported in the Marsh et al. (2007) paper and the DPE comments. Further, "age at onset" is not a relevant metric for evaluation in a mortality study when mortality outcomes are determined from death certificates. Cancer mortality **was** analyzed by Marsh et al. (2007) using multiple time-related factors (age at risk, age at hire, time since first exposure, etc.). These rigorous lagged and other time-related analyses supported the authors' overall conclusion that their study provided no evidence of an exposure-response association for chloroprene with lung or liver cancer.

- **One Panel Member commented that the "healthy worker survivor effect" (HWSE), may have biased the analyses reported in the Marsh et al. studies.**

Dr. Marsh provided a detailed overview of several alternative explanations for spuriously low baseline rates for lung and liver cancer observed in the Marsh et al. cohort study and concluded that the HWE cannot be the sole cause for the phenomenon. This conclusion would also apply to consideration of the HWSE for the same reasons.

Essentially, the potential for a HWSE as a possible explanation for non-monotonic trends in relative risks was considered through the evaluation of lagged analyses as discussed above. Lagged analyses[1] remove more recent exposure periods from all workers' cumulative exposure estimates and would adjust for longer employment periods for workers in Marsh et al. study (Checkoway et al., 2004). Therefore, lagged exposure periods reduce bias in the relative risk estimates for higher levels of cumulative exposure that may result from the preferential retention of healthier workers in the workplace. As discussed above, lagged exposure analysis showed no evidence of increased risk for cancer outcomes and did not materially change the interpretations of results from unlagged analyses.

- **One Panel Member commented that the periodic physical exams routinely given to workers at the Louisville plant included in the Marsh *et al.* study would have removed from the pool of eligible study members those individuals who were too ill to continue working.**

Workers in the Marsh et al. cohort study were followed for mortality outcomes through 2000 (1999 for the Grenoble, France plant) including workers with short duration of employment. There is no

[1] The use of lagged analyses to adjust for HWSE has been described in several research papers (Arrighi and Hertz-Picciotto, 1994; Gilbert 1982; Hertz-Piciotto et al., 2000).

evidence from the Marsh et al. study that any eligible study members had been omitted from the study population due to this or any other reasons.

- **One Panel Member also alluded to some unpublished NIOSH documents pertaining to the Louisville plant that should be evaluated as part of the analysis of lung and liver cancer rates.**

Selective incorporation of unpublished, non peer-reviewed materials should not be permitted until the USEPA establishes the validity or relevance of such materials.

Determination of Mode of Action

- **One of the primary arguments proposed by USEPA in support of a genotoxic mode of action and discussed by multiple Panel Members was the structural and biological activity similarities between chloroprene and 1,3-butadiene. In actuality, the genotoxic attributes of the two compounds are dissimilar when viewed across tests in common.**

Information	Chloroprene	1,3-Butadiene
Chemical is unequivocally mutagenic in the Ames Test (+/-S9)	**NO** Conflicting evidence as 2 of 4 studies were negative. Freshly prepared compound was negative (Westphal et al., 1994)[2]	**YES** Clearly positive in the base-pair substitution strain TA1535 +S9 (Madhousree et al., 2002)
Chemical induces point mutation in mammalian cell culture assays (+/-S9)	**NO** No mutation induction in V79 cells (+/-S9). Vinyl chloride, however, was mutagenic in this study (Drevon and Kuroki, 1979)	**YES** Weak but positive response at the TK gene in the mouse lymphoma assay (Sernau et al. 1986)
Chemical is genotoxic in standard *in vivo* genetic assays following inhalation exposure.	**NO** Target tissue toxicity observed but no increase in aberrations, SCEs or micronuclei in B6C3F1 mice up to 80 ppm (Shelby, 1990)	**YES** Dose related increases in chromosome aberrations, SCEs and micronuclei induced in B6C3F1 mice (Shelby, 1990)
G to C base substitution mutations in K-*ras* codon 61 are observed in mouse lung tumors	**NO** Excess of A to T transversion mutations (22/25 in codon 61) alleged responsible for increase in lung tumors (Sills et al., 1999).	**YES** Only G or C base substitutions were observed (Sills et al., 1999). No A to T *ras* mutations observed in codon 61 (or codon 12 and 13)

[2] Chloroprene was tested in TA1535 in four different studies: 2 of which were positive, while 2 were negative. The positive studies used a different approach in the administration of chloroprene than the two negative studies. The question, unresolved at this time, is if the application method allowed for the degradation of chloroprene to reactive dimers, which have been shown to be mutagenic (Wesphal et al. 1994).

- **Panel Members discussed the mutagenic activity of chloroprene but they did not seem to appreciate the lack of consistency in genotoxicity results. We believe that USEPA should reassess chloroprene to consider a non-genotoxic mode of action based on the following observations:**

    1. The results listed above challenge the weight of evidence presumption that chloroprene is genotoxic.
    2. Chloroprene is metabolized to an epoxide that binds with a high degree of specificity for G (guanine) and C (cytosine) DNA bases in a cell-free system (Munter et al., 2002, 2007). The USEPA interpretation that the excess A to T transversions found in lung tumor oncogenes is due to the mutagenic activity of the chloroprene epoxide conflicts with its established specificity for either G or C sites. Additionally, the absence of a dose-dependent increase in *ras* mutations concordant with the dose dependent increase in lung tumors (Sills et al., 1999) challenges the assumption that epoxide-induced ras mutations are the primary driver of lung tumors in the NTP mouse study.
    3. Scientists from the NTP and NIEHS have classified chloroprene as a non-genotoxic agent (Tennant et al. 2001; Prichard et al. 2003). Further, chloroprene did not produce tumors in Tg.AC and p53+/- transgenic mice strains (by the inhalation route) (Tennant et al. 2001; Prichard et al. 2003). The Tg.AC mouse screening test primarily responds to dermal applications of chemicals and does not necessarily distinguish genotoxic from non-genotoxic agents. In contrast, p53-null (heterozygous) mice respond well to genotoxic agents but not non-genotoxic agents (Prichard et al. 2002). The lack of a positive response in the p53-null mice is another piece of evidence that chloroprene is not acting by a genotoxic mode of action in the production of mouse tumors.
    4. Chloroprene produces hyperplasia in mouse bronchiolar and forestomach tissues. The incidence of hyperplasia increases with dose level, as does the incidence of alveolar/bronchiolar lung tumors.
    5. Results from the recently completed IISRP Genomics study (Himmelstein, personal communication) showed that chloroprene exposure results in dose related increases in cell proliferation in mouse lung bronchioles, but not in mouse lung alveoli.
    6. Induction of cell proliferation leading to hyperplasia with a secondary action of mutation expression is a scientifically recognized mode of action for toxic, but non-genotoxic carcinogens.

Toxicokinetics

- **Species differences in metabolism were previously published (Himmelstein, 2004a) but the Panel Members seemed to be unaware of key metabolism data.**

Himmelstein et al. (2004a) provided important information regarding species differences in metabolism. The reactions studied included total oxidative metabolism of chloroprene (which was used for PBTK modeling), simultaneous appearance of (1-chloroethenyl)oxirane, and detoxification reactions by microsomal epoxide hydrolase and cytosolic GST metabolism. Oxidation/hydrolysis ratios showed a 12-fold higher rate for mouse liver and 160-fold higher rate for mouse lung microsomes compared with human liver and lung microsomes, respectively (Himmelstein et al. 2004a). As noted in our written comments:

As a whole, the balance of reactive metabolite formation and detoxification across species appears to indicate that the mouse would be the most sensitive species, based on higher rates of epoxide formation, slower hydrolysis, and faster GSH conjugation, with perhaps the latter leading to an imbalance in glutathione (antioxidative) status and subsequently contributing to cytotoxicity.

In conclusion, these observations show that the mouse is not the most appropriate animal model for use in quantifying potential for cancer risk in the human.

- **One Panel Member made specific comments regarding the prevalence of polymorphisms in Glutathione S-Transferases (GST) in the US population and how these polymorphisms, specifically GST-null, may result in a sensitive subpopulation for cancer risk or disease**.

While it has been hypothesized that the presence of these null genotypes may increase the susceptibility of individuals to certain types of cancer or other diseases, several studies demonstrated no statistically significant association between the frequency of individual null genotypes and various cancers or diseases (Uzunoglu et al. 2006; Ho et al. 2006; Lizard-Nacol et al. 1999; Onaran et al. 2000; Bathi et al. 2009). Therefore, the presence of a GSTnull genotype does not always indicate an increased risk for disease.

Dose-Response Assessment – Noncancer

- **One of the Panel Members indicated that Chloroprene should be a Category 3 gas, not a Category 1, based on the USEPA (1994) RfC Dosimetry Guidelines.**

The toxicokinetics data that demonstrate systemic delivery of chloroprene provide support for Panel Member's position that chloroprene should be considered as a category 3 gas and not as a category 1 gas. This change in categorization impacts the dosimetric adjustment factors (DAFs) used to derive human equivalent concentrations (HECs) for the points of departure (POD_{HEC}) in Table 5-2 of the draft report. For the lung and systemic effects, we recommend that USEPA should use the PBTK model to estimate the POD_{HEC} values.

Dose-Response Assessment - Carcinogenicity

- **On the method of combining tumors, USEPA's practice of summing potency estimates for each tumor site assessed separately invokes an assumption of mutual exclusivity that is inappropriate and effectively results in double-counting of tumor-bearing animals.**

One of the authors of the Draft Toxicological Review provided the NAS (1994) report as justification for the approach used to sum unit risks. However, the NAS (1994) report also states that, "This procedure should be used unless specific data indicate that occurrence of the different tumor types within individual animals are significantly correlated." Application of the Kendall tau test for correlations to the individual tumor incidence data for chloroprene in both the male and female mouse suggests that significant correlations **are** present (correlation coefficients of ≥ 0.145 and p values ≤ 0.041); therefore USEPA's approach is not valid. We recommend that USEPA rely

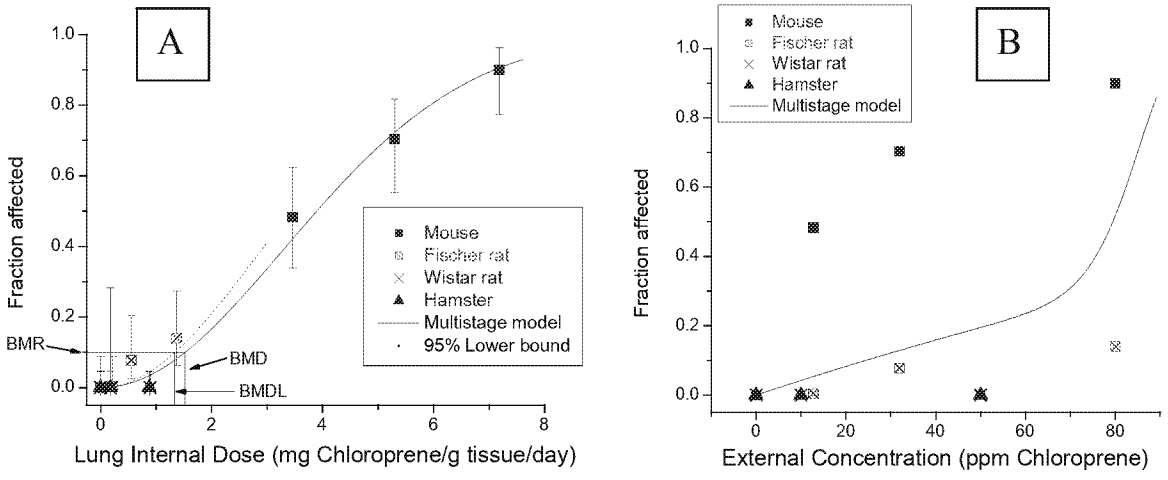
upon the most sensitive and relevant tumor type and that if any combining is to be performed, it should be done at the individual animal data level and not at the cancer potency level.

- **One of the Panel Members suggested the application of a mathematical approach that implied the "saturation" of tumor response could be modeled with a "Vmax and Km" approach that is empirical in nature and does not rely on PBTK modeling.**

The modeling approach presented at the Panel meeting appears to be based on the assumption that the overall shape of the tumor dose response curve was directly related to saturable metabolism of chloroprene. The approach discussed involved combining tumors and curve fitting using metabolic parameters (Vmax and Km) derived from the overall shape of the dose response curve. As mentioned in the DPE written comments, the combination of tumors as conducted by the Panel Member is not appropriate and can double count animals. Also, published kinetic data suggests that oxidative metabolism (as amount of metabolism per gram of liver or lung per day) is linear in the mouse up through the highest exposure concentration (80 ppm) used for the NTP inhalation bioassay (Himmelstein, 2004b). Therefore, use of a curve fitting approach that assumes metabolic saturation at a concentration of less than 80 ppm is inconsistent with the published literature on the metabolism of chloroprene.

- **One Panel Member discussed the continued use of external concentration in the derivation of the cancer potency estimate.**

As demonstrated in Himmelstein et al. (2004b), use of external concentration results in a cancer potency estimate that does not accurately predict observed tumor responses in exposed rats and hamsters, and therefore is not expected to reasonably predict tumor response in humans. These differences are readily visualized by comparison of the improved fit of the lung tumor dose response profiles for chloroprene using internal dose (panel A) versus external concentration (panel B) as shown below.



Use of a PBTK model-derived internal dose measure unifies responses such that all three animal species can be described on a single dose-response curve. The internal dose-response curve for lung tumors using all three species provides a scientifically sound basis for estimating potential risks to human populations exposed to chloroprene as explained in the written comments provided by DPE.

Comments made by Panel Members indicated confusion about why total metabolism of chloroprene would be a relevant dose metric for use in the dose-response assessment. Himmelstein et al. (2004a) measured total chloroprene oxidation (by disappearance kinetics). This captures the rate of metabolism to the known epoxide (1-chloroethenyl)oxirane and other unidentified (potentially reactive) metabolites. The "total" rate was scaled to the whole tissue, liver or lung, for incorporation into the *in vivo* PBTK model.

- **One Panel Member implied that the area under the blood concentration curve (AUC) of the identified reactive metabolite would be the more "correct" dose metric to use.**

The selection of the dose metric in Himmelstein et al. (2004b) was strongly influenced by early research showing that (1-chloroethenyl)oxirane is not detectable in the blood of mice or rats exposed to chloroprene by inhalation using the same highly sensitive gas chromatography-mass selective detection method used for the *in vitro* metabolism work (limit of quantitation ~0.06 μM (1-chloroethenyl)oxirane in solution). Furthermore, Hurst and Ali (2007) while investigating hemoglobin adduct formation, showed that *in vitro* incubation of the *S*- and *R*-enantiomers of (1-chloroethenyl)oxirane with fresh mouse blood resulted in significant preferential GST-mediated enzymatic reactivity of the S-enantiomer with GSH. Thus, in addition to formation *in vivo* and detoxification in the tissue of origin (e.g., lung or liver), any epoxide presented to the circulation would be subject to detoxification in blood. This finding helps explain the lack of detection in blood and pragmatically precluded the development of data to support a metabolite based sub-model and AUC estimates as discussed by the Panel. Finally, Clewell et al. (2002), which recommended reactive metabolite formation (per volume of tissue per time) as the most appropriate dose metric when all the individual reactive metabolites are not known, leads to the conclusion that use of total metabolism is both technically achievable and a defensible foundation for the chloroprene dose metric for dose-response assessment.

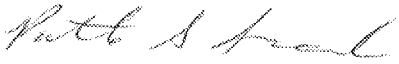
- **Panel Members discussed the potential lack of relevance of the mouse lung tumors to human health.**

The issue of the relevance of the bronchioloalveolar tumors in the mouse to human health was raised by multiple Panel Members, given the documented differences in metabolism between the mouse, rat and human. There are differences in the incidence of morphologic subtypes of lung carcinomas in rodents versus humans (both spontaneous and chemically induced). Rat and mouse lung tumors typically exhibit local epithelial cell hyperplasia, involving Clara or alveolar type 2 cells lining the alveoli, with subsequent adenoma formation (Witschi 2005; Maronpot et al. 2004; Richards and Oreffo 1993). These appear as distinct tumors with uniformly solid or, occasionally, papillary adenomatous patterns and may progress to bronchioloalveolar adenocarcinomas; however, they infrequently metastasize. In contrast, human lung tumors are characteristically either undifferentiated small cell or non-small cell carcinomas; among the latter, adenocarcinoma (most frequently observed), squamous cell carcinoma, and large cell carcinomas can occur. Most of these tumors originate in the conducting airways (loosely characterized as bronchogenic carcinomas) and are typically highly invasive. Bronchioloalveolar carcinomas represent <10% of the total human lung cancer types. For these reasons, the relevance of the observed rat/mouse bronchioloalveolar tumors may be questioned for relevance to humans.

The current USEPA (2005) Guidelines for Carcinogen Assessment provide a framework for consideration of the relevance to human health of observations in animals. As a part of this framework, the similarity of metabolic activation and detoxification for a specific chemical between humans and tested species should be considered. Given the differences between humans and rodents for lung cancer, the USEPA should reconsider whether selection of mouse lung tumors as the most sensitive species/effect for unit risk calculations satisfies the framework guidance.

In conclusion, we consider our collective comments provide support for the conduct of a linear and nonlinear dose-response assessment. Should USEPA disagree with this position, we request that USEPA include these analyses nonetheless so readers can appreciate the difference in outcomes these alternative approaches would produce in the risk assessment. In either case, a PBTK model must be used to develop HECs. We hope that you will thoughtfully weigh these points, along with our written comments, in your consideration of the Peer Reviewer comments.

Sincerely yours,



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